REMARKS

Applicants wish to thank Examiners Schmidt and LeGuyader for extending the courtesy of a telephone interview on December 11, 2002, and for the helpful discussion that ensued.

Applicants have carefully considered the points raised in the Office Action and the interview and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance, which is respectfully requested.

Status of the claims

Claims 23-49 are pending in the present application. Claims 1-22 were previously withdrawn from consideration as drawn to a non-elected invention. Claims 27, 29-31, 33 and 37 have been withdrawn as drawn to a non-elected species. Accordingly, claims 23-26, 28, 32, 34-36, and 38-49 are currently under consideration.

Applicants reiterate their request for inclusion of withdrawn species upon allowance of a generic claim, as permitted by 37 C.F.R. § 1.141(a).

Applicants have not dedicated to the public or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Rejection under 35 U.S.C. § 112, first paragraph

Claims 23-26, 28, 32, 34-36 and 38-49 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The claimed subject matter

In addressing Applicants' previous traversal of this rejection, the Examiner states that "Applicant does not address how the claimed RNA molecule goes from catalytically inactive to catalytically active, how the binding to c-myc is representative of binding to a substrate other than target, and further how the various probe compositions act to bind a target (such as c-myc?) or not bind a target such that the catalytic RNA molecule may still become catalytically active." Office Action, page 4. Applicants respectfully submit that these statements by the Examiner do not address the invention as set forth in the present claims.

(1) With respect to the Examiner's statement that the claims do not address "how the claimed RNA molecule goes from catalytically inactive to catalytically active," Applicants respectfully note that the claims require the RNA molecule to convert from a catalytically inactive to catalytically active conformation *upon binding to target*. Therefore, the conversion from a catalytically inactive to catalytically active form of the ribozyme is addressed in the claims.

(2) With respect to the Examiner's statement that the claims do not address "how the binding to c-myc is representative of binding to a substrate other than target," Applicants respectfully note that *the claims do not recite binding of c-myc to a substrate or a target*. "C-myc" is not recited in any of the pending claims. Further, the claims recite *binding to a target* and *catalytic action upon a substrate other than a target*, not "binding to a substrate." Therefore, the Examiner's statement concerning binding to c-myc does not apply to the currently-pending claims.

(3) With regard to the Examiner's statement that the claims do not address "how the various probe compositions act to bind a target . . . or not bind a target such that the catalytic RNA molecule may still become catalytically active," Applicants respectfully note that the claims recite that *catalytic action occurs upon binding of the catalytically inactive RNA molecule to the target*. Therefore, if the catalytic RNA molecule does not bind to the target, it does *not* become active. As disclosed in the specification, and as would be readily understood by one of

skill in the art, binding occurs either through base pairing between a polynucleotide target and sequences of the catalytic RNA molecule (see, *e.g.*, page 64, lines 22-23), or via interactions between sequences of the catalytic RNA molecule and a non-polynucleotide target, such as a protein, small molecule, or metal ion (see page 71, lines 17-19 and Figure 31) that are capable of stabilizing the catalytic RNA molecule in a catalytically active conformation.

Example VI

The Examiner further states that Example VI, which was previously discussed by Applicants as providing guidance regarding how to make and use the claimed invention is "primarily prophetic in nature." As discussed in the interview with Examiners Schmidt and LeGuyader, Applicants respectfully submit that whether or not an example is prophetic in nature is an insufficient basis for an enablement rejection. Providing a prophetic example does not render an invention nonenabled. See, for example, *Atlas Powder v. DuPont*, 750 F.2d 1569, 1577 (Fed. Cir. 1984), where the Federal Circuit held that "[u]se of prophetic examples . . . does not automatically make a patent non-enabling. The burden is on one challenging validity to show by clear and convincing evidence that the prophetic examples together with other parts of the specification are not enabling." Further, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, held that "[t]he first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance. . . . *[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.*" (emphasis added) An enablement rejection must be based on "sound scientific reasoning," not merely personal opinion of the Examiner (MPEP § 2164.05). A disclosure in a specification setting forth how to make and use an invention is presumptively enabled, absent evidence to the contrary (MPEP § 2164.04). The Examiner has provided no objective evidence to rebut this presumption.

Declaration of Brian Johnston

As further support of the enablement of the claimed invention, Applicants submit herewith a Declaration by Brian Johnston under 37 C.F.R. § 1.132, which sets forth data based on methods and constructs set forth in the specification, and shows that the invention works as claimed and is therefore enabled by the specification. The Declaration is attached as Exhibit A.

Using a hairpin ribozyme with catalytic and substrate (cleavage and ligation) sequences essentially as set forth in Figure 29 of the specification, a series of molecules having internally base paired sequences of 6-10 nucleotides in length were synthesized. Catalytic activity of the ribozyme was dependent on binding to a target molecule, TNF RNA, as shown in Figure 4 of the declaration, with an increase in target-dependent activity observed as the length of the internally paired inhibitory sequence increased. Only six internally base paired constructs were tested to find an optimal length of 8-10 base pairs which would render the catalytic activity of the ribozyme dependent on target binding. Testing of six constructs to find three that work well is not "undue experimentation."

A further working example is provided in the attached declaration. This experiment also included a ribozyme construct that included the core hairpin ribozyme sequences disclosed in Figure 29. As shown in Figure 5B of the declaration, addition of target resulted in activation of the ribozyme and catalytic cleavage of the substrate sequence. In absence of target (lane 8), no catalysis was observed. Thus, in this example, catalytic activity toward a substrate other than the target was dependent on target binding as claimed. Using the hairpin ribozyme core catalytic and substrate sequences, which are well known to those in the art and also represented in Figure 29 of the specification, along with the teachings of the specification regarding target-dependent catalysis, one of skill in the art would be able to practice the methods as claimed without undue experimentation.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(e)

Claims 23-26 and 28 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Bekkaoui et al. (U.S. Patent No. 6,136,533). Applicants respectfully traverse this rejection.

As discussed in the response filed on July 29, 2002 and in the telephone interview of December 11, 2002, the catalytic molecule disclosed in Bekkaoui (RNase H) is not allosterically regulated. In contrast, the present claims are directed to a catalytically inactive RNA molecule that is dependent upon binding to a target for catalytic action towards a substrate other than the target to occur. In the present invention, binding of the catalytically inactive RNA molecule to a target causes a change in conformation in the RNA molecule that is necessary for catalytic action upon a substrate. In contrast, the system disclosed in Bekkaoui uses a catalytic molecule (*e.g.*, RNase H) that is always in a catalytically active conformation and capable of catalysis upon a substrate (*e.g.*, RNA/DNA hybrid) *without activation by binding to a non-substrate molecule* as claimed. Bekkaoui does not disclose an allosterically regulated RNA molecule which adopts a catalytically active conformation upon binding to a non-substrate target molecule as presently claimed (*e.g.*, RNase H does not bind to a DNA target and thereupon become catalytically active toward an RNA substrate).

The Examiner states that "the claims do not specify what type of 'catalytic domain' the RNA molecules have" and that "[i]t is within reasonable interpretation of the claim language that a non-ribozyme catalytic event . . . is embraced by the claims." Office Action, page 9. As discussed during the telephone interview, a "catalytic domain," as recited in the claims, would be understood by one of skill in the art to mean a domain that is *within the molecule that causes the catalysis*. In the pending claims, the catalytic molecule is an RNA molecule that comprises (*i.e.*, includes) a catalytic domain within the RNA molecule itself. One of skill in the art would not interpret the language of the claims to embrace a "non-ribozyme catalytic event," as asserted by the Examiner. Further, Bekkaoui does not disclose the claimed element of a *catalytically*

inactive RNA molecule which comprises a catalytic domain, as required for this reference to be anticipatory.

The Examiner mentions that the disclosure of Bekkaoui "embrace[s] hairpin structures in the disclosed probes in col. 12, lines 56-65." Office Action, page 10. Applicants respectfully note that "hairpin structures" are not necessarily ribozymes and the hairpin structures in Bekkaoui are not disclosed as possessing catalytic activity. Further, the method disclosed within this section of the Bekkaoui specification requires providing a "cleavage means" in addition to the "hairpin structures." The cleavage means is not disclosed as requiring binding to a target in order for catalytic activity to occur (*i.e.*, allosteric regulation) as in the present claims.

In conclusion, Bekkaoui does not teach a method which includes allosteric activation of a catalytically inactive RNA molecule by binding to a non-substrate target molecule, and thus does not anticipate the claimed invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejection under 35 U.S.C. § 102(b)

Claims 23-26, 32, 38-40 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Stefano et al. (U.S. Patent No. 5,472,840). Applicants respectfully traverse this rejection.

In response to Applicants' arguments, the Examiner states that "Stefano does not need to teach the exact mechanism of action disclosed in the specification as filed" to be an anticipatory reference. Office Action, page 11. Applicants respectfully note that it is the elements of the *claims* that are under consideration in an anticipation rejection, not the "specification as filed." For an anticipation rejection, all of the elements of the claims must be taught in a single prior art reference. Therefore, the same "mechanism of action" as the *claimed* invention must be disclosed in Stefano for it to be anticipatory.

Further, the Examiner states that "the claims as broadly written, with comprising language, embrace additional method steps not explicitly recited in the instant claims." Office

Action, page 12. Applicants respectfully submit that this is not a proper basis for an anticipation rejection. As discussed above, all of the elements of a claim must be taught in a prior art reference for it to anticipate. That a claim may embrace additional steps does not alleviate the burden on the Examiner to show that all of the elements of the claim as written are disclosed in the allegedly anticipatory reference. As discussed in the response filed on July 29, 2002, Stefano discloses two different methods, neither of which includes all of the elements of the present invention as claimed.

One method taught in Stefano, shown, *e.g.*, in Figure 1, does not include a *catalytically inactive RNA molecule that comprises a catalytic domain*. In this method, target sequences form part of the catalytic domain, in contrast to the present invention, in which target sequences are separate from and not incorporated into the catalytic domain of the ribozyme. The catalytically inactive RNA molecule does not possess a catalytic domain in the absence of target sequences, as in the present claims.

The other method described in Stefano, shown, *e.g.*, in Figures 3 and 4, does not include *allosteric activation of a catalytically inactive RNA molecule upon binding to a target*. In this method, the target sequences are responsible for localization of the ribozyme pieces, rather than activation of catalytic activity. The two-piece catalytic RNA complex is in an active conformation independent of target binding and thus does not become active only upon binding to the target, as presently claimed.

Neither of the methods disclosed in Stefano includes all of the elements of the presently-claimed invention, as required for an anticipation rejection. None of the methods disclosed in Stefano teach a method which includes *target-dependent activation of a catalytically inactive RNA molecule comprising a catalytic domain* as claimed.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 367592000100. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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